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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/524,454	BERG ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,6,8-10 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,6,8-10 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 9/6/05, are acknowledged.

2. Claims 2, 4, 6, 8-10, and 22 are pending and being acted being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2, 4, 6, 8-10, and 22 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could be used for expressing a molecule on a cell, said method comprising photochemical internalization wherein the molecule is sufficient to generate an immune response, for the reasons of record.

As set forth previously, the breadth of the claims, in light of the limited disclosure of the specification, would not allow one of skill in the art to practice the invention as broadly claimed without an undue amount of experimentation.

First note that it is clear that the photochemical method (employing certain disclosed agents) of the instant application (and the prior art) can be used to internalize exogenous molecules. The method of the instant claims, however, requires more. The claimed method requires the surface presentation of a sufficient amount of the internalized molecule to generate an immune response.

It is well-known in the immunological arts that only certain antigen presenting cells are capable of presenting antigens and generating an immune response. See, for example, Janeway et al. (1994) wherein it is taught that in addition to antigen presentation, costimulation that can only be provided by B cells, macrophages, or dendritic cells, is required for the generation of an immune response. Accordingly, it appears that the method of Claims 2-5 and 7-11, employing any cell capable of photochemical internalization, could not be performed without an undue amount of experimentation.

Further regarding the breadth of the claims, the specification discloses only the actual use of $AlPcS_{2a}$ and $TPPS_{2a}$ as photochemical internalization agents. Claims 2-7 and 9-11 comprise either no limitations regarding photochemical internalization agents, or as in the case of Claim 7, are drawn to whole classes of agents. The disclosure of two related species of agents cannot be considered to be reasonably

sufficient to enable the method of the instant claims to be performed with any of the essentially unlimited number of disclosed families of chemicals without an undue amount of experimentation.

Finally, it remains the Examiner's position that the disclosure of the specification does not sufficiently demonstrate the required limitation that the claimed method be capable of inducing sufficient MHC class I presentation of an antigen to generate an immune response. As set forth previously, the specification fails to disclose any actual Class I MHC presentation. Indeed, the only experiment which might demonstrate any sort of surface presentation, Example 3, clearly demonstrates the opposite, the triangles of Figure 4 show a *lack* of antigen on the surface of the cells.

Applicant's arguments, filed 9/06/05 have been fully considered but they are not persuasive. Applicant reviews the invention of the instant claims. Applicant asserts that the photosensitizing agents are fully enabled by the specification. Applicant argues that expression of an antigenic peptide on a full range of cells is enabled by the specification and indicates confusion in the Examiner's assertion that only certain cell types can stimulate an immune response. Applicant argues that the specification at page 9 is directed to the stimulation of *any* aspect of an immune response (emphasis added by Examiner).

Applicant is advised that the specification fails to show the expression of any antigenic peptides on the surface of any cells, i.e., no cell surface expression of any sort is shown. Accordingly, an argument that the specification is fully enabled for the expression of an antigenic peptide on a full range of cells comprises no more that an attorney's assertions and is not persuasive. Regarding the argument that the specification at page 9 is directed to the stimulation of *any* aspect of an immune response (and thus, the claims are intended to encompass the stimulation of any/all types of immune responses), clearly, at least the stimulation/generation of a primary immune response in naïve T cells, which is encompassed by the method of instant claims, is not enabled as set forth previously.

Applicant argues that specification enables the expression of antigenic peptides on a variety of cell types and cites Example 2. Applicant further argues that Claim 6 is defines the types of cells used in the claimed method and cites page 9, lines 21-25 as enabling the claimed method.

Regarding Example 2, said example was discussed in the action of 4/01/05, reiterated here: In regards to Example 2, the methods of the example are not the methods of the instant claims, nor are they representative

of the scope of the methods of the instant claims. In the example, a single cell type is loaded with a particular antigen; said loaded cell is then used in a CTL ^{51}Cr release assay. The CTLs employed in a ^{51}Cr assay are primed/activated CTLs and are not representative of the generation or stimulation of an immune response, i.e., the method of the instant claims. See, for example, Janeway et al. (1994) wherein one of the fundamental rules of cellular immunology is taught, i.e., that the generation of an immune response from naïve T cells *requires* professional APCs. Clearly then, the ^{51}Cr assay of Example 2 employs primed/activated CTLs and does not comprise the generation or stimulation of an immune response. Note also that the specification discloses that the assay of Example 2 is the assay of Fossum et al. (1995) in which primed CTLs were employed. Accordingly, it remains the Examiner's position that given the breadth of the claimed method, i.e., the employment of *any* cell type in the production of cells capable of generating an immune response (in defiance of one of the fundamental concepts of cellular immunology), the specification provides insufficient support and is not enabling.
Further, because the example comprises no appropriate controls, the skilled artisan would know that no conclusions could be drawn based on the disclosed results. Regarding Claim 6, first note that the limitations of the claim apply only to Claim 6, regardless, neither all types of lymphocytes nor all types of cancer cells are capable of the stimulation/generation of any/all types immune responses as are encompassed by the instant claims. Finally, it is unclear how the minimal disclosure at page 9, lines 21-25:

> "Antigen-presenting cells are known in the art and described in the literature and include for example, lymphocytes (both T and B cells), dendritic cells, macrophages etc. Others include for example cancer cells e.g. melanoma cells.",

enables the claimed invention.

5. Claims 2, 4, 6, 8-10, and 22 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. **Note:** the rejection was previously of Claim 7 only, however, the limitations of Claim 7 have been amended into independent Claims 2 and 22, thus, the rejection has been extended to all pending claims.

There is insufficient written description to show that Applicant was in possession of "a lysomotropic weak base" of "a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, or tetracycline".

As set forth previously, "the specification fails to disclose any species of the claimed reagents. Further, no definition is provided that would limit "lysomotropic weak bases". Accordingly, one of skill in the art would conclude that

the specification fails to disclose a representative number of species to describe the claimed genus.

Applicant's arguments, filed 9/06/05 have been fully considered but they are not persuasive. Applicant notes that the genus of photosensitizing agents encompassed by the claims has actually been broadened by the deletion of "thereof. Applicant argues that the bases are well-known in the art and again cites references previously submitted in support.

It is unclear how the broadening of the claims (to encompass *all* lysomotropic weak bases) can actually provide a better written description of the claimed subject matter. The specification still provides an inadequate written description of the lysomotropic weak bases of a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, or tetracycline. Again, a review of the references fails to show that the lysomotropic weak bases in question were well-known in the art as they are not the subjects of the references. And with the newly broadened claims, the issue of which of the lysomotropic weak bases now encompassed by the claims would function in the method of the instant claims might now be raised.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 2, 4, 6, 8-10, and 22 stand rejected under 35 U.S.C. 102(b) as being anticipated by WO96/07432 (IDS). **Note:** Claim 22 was inadvertently excluded due to typographical error from the previous rejection; clearly, the cancer cell of Claim 23 was a species of the generic cell of Claim 22.

As set forth previously, WO96/07432 teaches a method of expressing an antigenic molecule on the surface of a viable cancer cell, said method comprising:

contacting said cell *in vitro* with said antigenic molecule (including a vaccine component, a molecule capable of stimulating an immune response, and a peptide, also including an antigen bound to a carrier molecule) and with a photosensitizing agent (a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, tetracycline, and a lysomotropic weak base thereof, including $TPPS_4$, $TPPS_{2a}$, and $AlPcS_{2a}$, also including a photosensitizing agent bound to a carrier molecule),

wherein said molecule and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; and irradiating said cell with light of

a wavelength effective to activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing said molecule into the cytosol of the cell, without killing the cell by irradiation,

wherein, said released antigenic molecule, or a part thereof of sufficient size to generate an immune response, is subsequently presented on the surface of said cell by a class I MHC molecule (see particularly the claims). Note that reference does not specifically state that the method results in the cell surface expression of the antigen in MHC Class I, however, the reference teaches the same steps as those of the instant claims, thus, said same steps would inherently result in the same outcome, i.e., the claimed method of the expressing an antigenic molecule on the surface of a viable cell.

Applicant's arguments, filed 9/06/05 have been fully considered but they are not persuasive. Applicant argues that the reference does not disclose the presentation of peptide antigen on the surface of a cell resulting in the stimulation of an immune response.

As an aside, note that the instant specification also fails to show the presentation of peptide antigen on the surface of a cell resulting in the stimulation of an immune response. Regardless, the same reagents and steps of the instant claims are employed and performed in the reference. It is unclear how the method of the instant claims would not result from the method of the reference.

Applicant argues that inherency must be supported by factual and technical grounds. Specifically, Applicant argues that the reference contemplates the use of cytotoxins and other molecules that may not be antigenic and may not be displayed on the cell surface.

Applicant's argument seems curious in light of the fact that the instant specification itself provides essentially no enablement for the claimed method. It is unclear how the method of the prior art would not be enabled but the method of the instant claims would be. Also note that the instant claims recite no limitations on the peptide antigens or cell types (with the exception of Claim 6, discussed above) encompassed by the method of the instant claims. Note that the reference claims the use of proteins/peptides, only one of which need be antigenic, (transferrin and gelonin are both taught by the reference and both are known in the art to be antigenic) in only a single context to anticipate the antigenic peptides of the instant claims.

8. The following are new grounds for rejection necessitated by Applicant's amendment.

9. Claims 2, 4, 6, 8-10, and 22 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) a molecule comprising an antigenic peptide (Claims 2 and 22),

B) a lysomotropic weak base (Claims 2 and 22).

Applicant cites the original claims 5, 7, and 11 and pages 9 and 10 of the specification in support of the new claims.

No support has been found for the specific combinations of limitations set forth above.

Regarding A), original Claim 5 recited an antigenic molecule that is a peptide. New Claims 2 and 22 recite an antigenic molecule that comprises a peptide. Thus, while the original claim was limited to being a peptide, the new claims comprise a molecule that encompasses a peptide and anything else, e.g., a peptide linked to sugar or lipid.

Regarding B), the original specification and claims disclose only lysomotropic weak bases of porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, tetracycline, e.g., Claim 7 and page 12, but not the much broader genus of *all* lysomotropic weak bases as is now claimed.

10. No claim is allowed.

11. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action

is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

11/24/05

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